Improved Governance and Research Capacities in Diagnostics for Infectious Diseases of the Liberian Medicines and Health Products Regulatory Authority (IGORCADIA)

Coordinator: Dr Alfredo Mayor, ISGlobal

Research and development of preventive and therapeutic interventions for emerging pathogens have been difficult to maintain in the past once outbreaks come to an end. In Liberia, much of the research on Ebola ended when the outbreak faded in 2016 even though sustained funding could have led to further the development of vaccine candidates and other therapies for Ebola. One major challenge is to maintain the continuum of studies and the preparedness of research sites, including infrastructure and staff capacities, for future clinical studies that can lead to an effective vaccine and/or treatment against prevalent infectious diseases in West Africa.

To date four clinical trials aimed at developing vaccines and therapies against Ebola virus disease (EVD) were started in Liberia.[1] Evaluations of novel treatments for EVD can only take place while the Ebola virus continues to circulate. The end of the epidemics was welcome, although the halt in new infections posed a challenge for clinical trials that relied on large cohorts of patients to produce results.

It is essential to guarantee that other studies of potential treatments and vaccines will continue to deliver preventive and treatment tools for the inevitable future epidemics. At-risk countries need to be prepared for these future epidemics with a much faster and effective response. Preparedness should not only focus on Ebola but also on other potentially lethal infectious diseases that occur in Sierra Leone and Liberia, such as Lassa Fever. Preparedness should include research for development of diagnostics

[1] Clinical Trial to Evaluate the Efficacy and Safety of Convalescent Plasma for Ebola Treatment (EVD001) (NCT02333578); the Rapid Assessment of Potential Interventions & Drugs for Ebola (RAPIDE-BCV) (PACTR201411000939962); the Putative Investigational Therapeutics in the Treatment of Patients with Known Ebola Infection (NCT02363322); the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) (NCT02344407).

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for neglected and poverty-related infectious diseases that affect the most vulnerable people as well as for new epidemics that could affect Liberia aided by increased commercial air travel and by the reported occurrence of vector *Aedes aegypti* in West Africa.

Clinical trials should produce results rapidly to ensure maximum benefit and minimum harm, and they need to be acceptable to those delivering and receiving care under very challenging conditions. One of the main challenges for those delivering care at the Ebola Treatment Units was the lack of rapid tests with reliable sensitivity and specificity for Ebola and other infectious diseases. At the start of the epidemic, point-of-care diagnostics such as the Cepheid Xpert® Ebola Assay, that has a demonstrated high analytical sensitivity and specificity for the detection of EBOV in whole blood, were not available for rollout at the Ebola Treatment Units.

In Liberia, the clinicians delivering healthcare to Ebola patients had to rely on external laboratories, such as the National Reference Laboratory (NRL). However, the NRL dedicated its resources and staff to run tests for Ebola only. Many tests for many other infectious diseases such as MDR-TB or Lassa were not done, hindering the capacity to make a proper differential diagnosis. Due to the lack of laboratory capacities, poor infrastructure, and the very limited number of reagents and experienced staff, investigators implementing clinical trials in the affected countries had to invest large amounts of time and resources importing diagnostics equipment and reagents, bringing in healthcare staff, and building new infrastructures to set up laboratories for the testing of volunteers' and patients' samples.

Challenges and scope

Trials will reassume rapidly when and where the next Ebola outbreak or new mosquito-borne viral epidemics occurs. Limited laboratory infrastructure, laboratory capacities and availability of licensed diagnostics will make difficult the conduct of research in the region. EVD clinical trials will be challenging, as vaccine and drug formulations have yet to be optimized, and there is need to ensure that proper diagnostics are used to make differential diagnosis with other hemorrhagic fever viruses, to properly diagnose concomitant infections so that proper healthcare is offered to trial volunteers, and to test the safety of samples or blood products to be used for transfusion.

For life-threatening diseases, vaccines and drugs can be only licensed on the basis that adequate, well-managed and well-controlled trials that predict a clinical benefit have been conducted. Without a precise understanding of fundaments of diagnostics research and good laboratory practices, the robustness of clinical trials may be compromised. On the other hand, efforts must be done to ensure that regulatory authorities have the capacities to perform their function of approving and closely monitoring trials' diagnostics-related activities. Regulation of in vitro diagnostics has been neglected in many countries in sub-Saharan Africa.

In preparation for future trials in future epidemics, Liberia needs to ensure that subjects with suspected or confirmed infections need have access to most accurate diagnostics. Healthcare providers must have access to most reliable point-of-care diagnostics in order not to disrupt their clinical activities and to reduce the risk of patients' attrition or risk of appearance of clinical complications or opportunistic infections. In the absence of properly equipped government reference laboratories inside the country, regulatory authorities need be strengthened so they develop regulatory framework to revise and authorize protocols and to monitor conduct of diagnostics research as well as the use of diagnostics in clinical trials. Capacities for clinical trials and diagnostics research must be ready for rapid implementation when needed.

In this sense, there is an urgent need in Liberia to build the regulatory capacity of the LMHRA. Firstly, training on good clinical practice, good laboratory practice, fundaments of medical ethics and diagnostics research within the agency are necessary.

Second, there is a need to define and build common goals between LMHRA and other national health research ethics committees and regulatory authorities in the region. Training, communication, and networking are key strategies to show that LMHRA has developed its capacity to oversee the use of diagnostics in research and the research on diagnostics, as well as to accomplish its mandate to

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regulate the use of diagnostics. Additionally, skills in governance need be fostered to ensure that LMHRA is able to engage other stakeholders in implementing regulations and in promoting a rational use of diagnostics.

Third, trust needs to be built. During the Ebola many communities distrusted the national health system. There is need to raise awareness of a rational use of diagnostics, as the use of counterfeit or substandard diagnostics may result in incorrect therapies being prescribed, an increase in drug resistances, and even death.

AIM and Objectives

The purpose of IGORCADIA is to strengthen the LMHRA regulatory mandate and capacities in the use of diagnostics in research and on research on diagnostics for infectious diseases. IGORCADIA aims to train and capacitate LMHRA staff to develop their regulatory framework; to improve LMHRA governance skills and working relationships with national and regional stakeholders; to build synergies with national and regional health research ethics committees to revise and monitor diagnostics research proposals; to consolidate authority staff skills and knowledge in diagnostics research and ethics in medical research; and to acquire knowledge and tools to raise awareness on a more proficient and rational use of diagnostics for infectious diseases. Specific objectives are:

1) To strengthen LMHRA capacity as a Governmental organization with mandate to regulate, register and license individuals/entities engaged in the importation, storage, and use of diagnostics for infectious diseases alongside supervision and inspection of access to and use of diagnostics in the frame of clinical trials and clinical research.
2) To build LMHRA capacity in revision, design, conduct, analysis and dissemination of research on novel diagnostics for poverty-related infectious diseases with epidemic potential in Liberia (i.e. Lassa, Ebola, HIV, Tuberculosis, Hepatitis C, Malaria, Zika).
3) To enhance LMHRA's capacity to establish inter -agencies collaboration through skillful sensitization, mobilization, and active engagement of relevant authorities and civil society in methods of appropriate handling and rational use of diagnostics.

IGORCADIA is coordinated by the Barcelona Institute of Global Health (ISGlobal) (Spain) in partnership with the Liberian Medicines and Health Products Regulatory Authority (LMHRA), the NGO Juan Ciudad Foundation (FJC) (Spain) and the Saint Joseph's Catholic Hospital in Monrovia (SJCH) (Liberia).

WORKPLAN

The project objectives will be achieved by, primarily, the conduct of literature, policies and regulations search and training activities to revise LMHRA regulatory framework and adapt it to internationally recognized standards; to enable pathways for networking at national and regional level; to encourage participation in training programmes offered by regional centers of regulatory excellence (RCOREs); to develop the capacity of LMHRA staff and key stakeholders in most widely used designs of diagnostics research; to gather information to raise awareness on the need to conduct research to validate diagnostics in Liberia for the infectious diseases that are most prevalent or most threatening; and to strengthen collaboration with the reference laboratory at SJCH for LMHRA to establish a platform to conduct diagnostics research.

The organization of **Regulatory Framework Development** activities will be supported by the Quality Assurance Officer at LMHRA (Mr Alexander George):

- **Desk review of regulatory framework** (Months 2-5). This activity will involve landscaping the documentation produced by other regulatory authorities, contacting colleagues from these authorities, and compiling all pertinent documentation. A search, compilation and revision of regulations validated and recommended by the World Health Organization (WHO), the WHO Prequalification Team–Diagnostics, the West African Health Organization (WAHO), the New

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Partnership for Africa's Development (NEPAD), the African Medicines Regulatory Harmonization (AMRH) programme, the African Society of Laboratory Medicine (ASLM), and the Food and Drugs Authority of Ghana (FDA-Ghana) will be made. This documentation will be useful for LMHRA to develop its own regulatory framework for the revision, authorization, implementation and monitoring of research on diagnostics for infectious diseases.

- **LMHRA Technical Working Group (TWG)** (Months 6-24). A TWG composed of LMHRA, SJCH, and ISGlobal staff and invited key members to the NHREC will work in revising selected body of regulatory documentation:
  - i) To facilitate a transparent process for research institutions to apply for revision and approval, to conduct, and to supervise and report to the LMHRA on any clinical research proposals that aim to validate novel diagnostics or that aim to import diagnostics that are licensed elsewhere for research purposes.
  - ii) To communicate with all national and institutional ethics committees in Liberia (i.e. NHREC, LMHRA, UL-PIRE) on regulations, guidelines and procedures developed on the use of diagnostics for research purposes in Liberia.
- **Information and Communication on Regulatory Framework** (Months 6-24). In improving communication and information exchange between LMHRA and key policy-makers in Liberia, information and communication technologies will be used to update legislators on new diagnostics for infectious diseases available on the Liberian market; on diagnostics incorporated to the WHO Prequalified In Vitro Diagnostics list and eligible for UN & WHO Member States procurement; changes in international, regional and local regulations for importation, storage, marketing, distribution and use of diagnostics and derived product for research purposes; and advances in the region promoted by RCOREs in the field of novel diagnostics for infectious diseases with epidemic potential.

The organization of a **Training on Diagnostics Research** will be guided by ISGlobal Department of Training and Education (Dr. Núria Casamitjana):

- **Training Programme on Diagnostics Research** (Months 6-12). Five three-days workshops (Good Clinical and Laboratory Practice; Fundaments of Health Research and Medical Ethics; Quantitative Approaches in Diagnostics Research; Social Approaches in Diagnostics Research) will be conducted. This training will include content on validation of new diagnostic tests in reference to The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. Ten LMHRA trainees and five SJCH trainees will attend.
- **Conduct of quantitative research** (Months 12-23). In order to evaluate acquisition of competencies in diagnostics research, seven to nine of the trainees will design a quantitative research. Topics of interest identified include, but are not limited to:
  - iii) Field-testing of quality control of diagnostics for infectious diseases,
  - iv) Exercise to assess sensitivity of unlicensed, unregistered and presumably counterfeit diagnostics in use in Liberia,
  - v) Evaluate the accuracy (sensitivity and specificity) of a novel diagnostics test for malaria infection.
- **Formative research on the use of diagnostics in public spaces** (Months 12-23). Another seven to nine of the LMHRA and SJCH trainees will design a social research. Topics of interest that have been identified include, but are not limited to:
  - i) Understand to which extent diagnostics are employed in public spaces others than healthcare settings,
  - ii) The perception on street-used diagnostics being counterfeit and how their use are driving demand of preventative or curative care for infectious diseases,
  - iii) Feasibility and acceptability of integrating post-market surveillance as per WHO Prequalification Team-Diagnostics recommendations in MoHSW facilities,
  - iv) Exploration on possible misuse of medicines (e.g. prescription of antimalarial in cases with a rapid malaria diagnostic test negative result).
- **Strengthening SJCH Laboratory capacities** (Months 11-14). This activity aims at

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consolidating SJCH as a reference laboratory partner for LMHRA. The SJCH had their staff GCLP-trained thanks to SELeCT Project (EDCTP-CSA-Ebola-334). Recently, the SJCH opened a new PCR testing area. In order to ensure that the quantitative research is done with no complications, the PCR area will be improved with equipment, reagents and other fungible materials. Two consultants will facilitate education on new diagnostic technologies as well as refreshment hands-on training on quality control and calibration of RT-PCR and PCR testing. LMHRA and SJCH laboratory staff will take part. Additionally, the SJCH Laboratory Supervisor will training either at the ISGlobal Laboratory in Barcelona or at an ISGlobal collaborating center at the University of Ghana or at any of the research centers members to the EDCTP-funded WANETAM.

The organization of **Networking** activities will be guided by LMHRA Managing Director (Mr David Sumo) with support from ISGlobal:

- **Diagnostics Steering Committee (DSA) meetings** (Months 6-22). This activity will contribute to improve advocacy and governance skills at LMHRA. A DSA will enable a political environment favorable to the implementation of policies for diagnostics research. A total of twenty relevant stakeholders (e.g. Pharmacy Board, University of Liberia, Liberia Medical and Dental Council, etc) will be invited to become members to this DSA. Key stakeholders from the region (e.g. WANETAM; Food and Drug Authority of Ghana; University of Ghana-School of Public Health, etc) will be also invited to attend.
- **Joint training on ethics** (Months 12-18). The LMHRA has a Medicines and Health Products Research Coordinating Committee (MHPRCC), informed by the LMHRA Institutional Review Board. Working relationships are already established between the LMHRA and the various national and institutional ethics committees in Liberia because the LMHRA requests researchers to obtain ethics approval prior to issuing regulatory approval for clinical trial proposals. To develop a fully functional and harmonized system and to enhance LMHRA institutional capacities to revise protocols that involve development and testing of diagnostics, a hybrid training programme on ethics will be developed. This programme will include a 3-days workshop in Monrovia followed by remote eLearning support using ISGlobal Moodle-based eLearning platform. The focus of this training will be on ethics around diagnostics research and development. Ten LMHRA, two SJCH staff and five invited members to the NREB will be invited. This training will serve to establish synergies and working relationships with NREC.
- **Training at RCORE FDA Ghana** (Months 7-13). Three LMHRA staff will receive training on: a) evaluation and appropriate use of diagnostics and innovative point-of-care testing, b) the institutionalization of the importance of accurate and reliable diagnosis, and c) strengthening laboratory networks, surveillance and quality.
- **Presentation of Outputs at International Conferences** (Month 6-24). Two LMHRA and one ISGlobal representative will participate at the 2018 African Society of Laboratory Medicine and at the 2018 9th EDCTP Forum to share the progress and outcomes of the project as well as to network with other regulatory authorities' representatives and key diagnostics and microbiology associations and firms' representatives.

More info:

www.igorcadia.org

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